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1126 September 9, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20857

SUBJECT: Docket 99D-0193
Proposed Rule: Supplements and Other Changes to an Approved Application

Dear Sir or Madam:

We refer to the June 28, 1999 Federal Register notice requesting comments on the proposed rule, "Supplements and Other Changes to an Approved Application," Docket No. 99D-0193. Reference also Janssen's August 26, 1999 comments on Docket no. 99D-0529, "Draft Guidance for Industry on Changes to an Approved NDA or ANDA." As discussed at the August 19, 1999 FDA/Industry meeting on this topic, we concur with PhRMA's and PDA's assessment that the documents, while progressive in some sections, do not meet the intent of Congress in the manufacturing changes sections of FDAMA, to relieve regulatory burden. We urge the Agency to incorporate the industry suggestions identified and discussed at the August 19 meeting into a final, comprehensive document, rather than focusing on meeting an imposed deadline with a regulation that does not address the Congressional intent of this section of FDAMA. Our general and specific comments on the proposed rule are appended, a copy of which will be e-mailed to Nancy Sager, as requested at the meeting.

We thank the Agency for the opportunity to provide comments on this proposed rule and look forward to a continuing dialog as the Agency finalizes its guidance and rule on this topic. Please do not hesitate to contact me at (609) 730-3081 if you have any questions regarding our comments.

Sincerely,

S Alexander

Sheila Alexander
Asst. Director, Technical Regulatory Affairs

99D-0193

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General Comments
We concur with PhRMA's and PDA's recommendation that the term "validate," used throughout the document, should be revised to "assess," "evaluate" or "confirm," to avoid potential confusion with the cGMP definition of "validation," which would not apply here.

314.70(a)(6) - listing all CMC changes in the supplement/annual report cover letter
We recommend that this requirement be more flexible, such that the summary of changes may appear in an introductory section of a supplement or at the beginning of the CMC section of an annual report. We note that annual report cover letters are typically very brief and, often, are not intended to include a comprehensive summary of the content of the annual report. Such a requirement would result in the cover letter becoming a voluminous document, which simply duplicates the information in the annual report itself.

314.70(b)(2)(i) - changes in qualitative or quantitative formulation of the drug, including inactive ingredients
We note that the quantitative levels of inactive ingredients are covered in certain SUPAC guidances and list percentage ranges over which the components can be varied. For example, a change of up to 5% in an excipient is considered a minor change in SUPAC-SS and may be reported in the Annual Report. The revised regulation should follow the standards set by SUPAC in this regard.

314.70(b)(2)(iii) - changes that may affect sterility assurance
As discussed at the FDA/Industry meeting, we suggest clarifying that these are changes with "potential *negative* (or adverse) impact on sterility." Addition or substitution of aseptic processing steps may not negatively impact sterility assurance, and in fact could enhance sterility assurance. In these cases, PAS would not be warranted.

314.70(b)(2)(iv) - changes in synthesis or manufacture of the drug substance (DS)
Changes in DS synthesis route, which occur prior to the formation of key intermediates, should not be regarded as major changes, since the potential to impact the quality, strength, identity and purity of the final product is low. As such, these should not be classified as prior-approval changes.

314.70(b)(4) - public health reasons or "extraordinary hardship" for expedited review
As discussed at the FDA/Industry meeting, please consider adding mandatory vendor-imposed changes (without sufficient reaction time) to the list of "not reasonably foreseen" events. An example of such an event is a vendor's decision to discontinue manufacturing a certain component and close its manufacturing plant, without an alternative source/site.

314.70(c)(6)(ii) - change in size and/or shape of a non-sterile DP container (not solids)
We recommend that the phrase "without a change in the labeled amount of product" be removed from this section, as it increases regulatory burden. A corresponding change in fill quantity, along with change in container size, is expected and readily acceptable.

314.70(d)(2)(i) - change made to comply with an official compendium that is consistent with FDA requirements and provides increased assurance that....
The criteria that the change be "consistent with FDA requirements" and "provide increased level of assurance" represents an increased regulatory burden over the existing 21 CFR 314.70(d)(1). In addition, it dilutes the status of the USP/NF as official US compendia. It has the potential to produce inconsistent standards for the same drug, depending on source. Finally, it can impose a

competitive disadvantage to innovator firms who must comply with USP and (possibly more stringent) FDA requirements, while subsequent manufacturers may conform only with USP.

314.70(d)(2)(iv) - change in size and/or shape of a non-sterile solid DP container
We recommend that the phrase "containing the same number of dosage units" be removed from this section, as it increases regulatory burden. A corresponding change in fill quantity, along with change in container size, is expected and readily acceptable.

314.70(d)(2)(vi) - expiration dating extension based on full production batches
Please clarify that the batches need not be saleable, if they are fully representative of commercial material.

314.70(d)(3) - application holder must submit in AR: i) statement that effects of change have been validated, ii) description of changes, including areas involved, iii) date each change was made, cross-reference to relevant validation protocol/SOPs and data from studies performed to evaluate the effect of the change
This part of the proposed rule presents undue additional burden to the applicant. i) We again stress the use of the term "assess" in place of "validate." Assessment is guaranteed in the filing via provision of relevant supportive data. Restating this fact of compliance with regulatory requirements is redundant. ii) Specifying details of exact "areas involved" is inappropriate, since this information is not typically part of the NDA filing, but subject to Field inspection. Therefore, we do not believe it should be provided in the annual report. iii) Annual reports, by nature, specify a period during which a reported change was made. Specifying an exact implementation date would present undue burden to both manufacturing and regulatory affairs personnel. This is also not practical for changes affecting multiple sites. It is our understanding that once assessment is complete, an annual-reportable change may be implemented and reported in the next scheduled annual report. Reference to validation protocols and SOPs are considered a site-GMP issue, subject to Field inspection, and not appropriate for submission in a post-approved supplement or annual report.

314.70(e) - protocols to demonstrate lack of adverse effect
As discussed at the FDA/Industry meeting, we urge the Agency to consider a CBE-30, rather than PAS filing mechanism for these protocols, based on their expected brevity for review. Also, we support the position that such protocols should be fileable for approval in *original* NDAs, in addition to post-approval filings. We would like to operate with the understanding that, if a relevant protocol is subsequently published in an official compendia or Agency document (guidance, et al), the less burdensome protocol may be applied. Finally, we would welcome the Agency's involvement in drafting "common" comparability protocols, so consistent requirements are imposed on all sponsors. Alternatively, Agency guidance on comparability protocol format/content would be helpful.

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